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REMARKS

Information Disclosure Statement:

Applicants note that the Examiner has signed, but not initialed, all of the references that were cited in Applicants' 1449. For the Examiner's convenience, duplicate copies of the references will be sent by separate mailing shortly to ensure that the references are properly considered.

Objection to the Specification and Rejection of Claims 1, 3-17, 19-21, 24-26[sic], 38 and 70 Under 35 U.S.C. § 112, First Paragraph:

The Examiner has maintained the rejection of Claims 1, 3-17, 19-21, 24-26[sic], 38 and 70 under 35 U.S.C. § 112, first paragraph, contending that the specification does not reasonably provide enablement for a conjugate comprising **any** antigen. The Examiner contends that none of the other antigens listed in the specification have been shown to elicit any type of immune response in the claimed compositions, and that it is entirely unclear how other antigens will behave *in vivo* when used in the claimed compositions. The Examiner asserts that the later published articles submitted with the last Amendment and Response do not address compositions falling within the scope of the claims, because the immunoregulatory compositions described in these publications, and administered to animals, allegedly do not include mannose receptor bearing cells (i.e., the results allegedly merely show the induction of a T cell response following administration only of mannan-antigen conjugates). A similar argument is made with respect to the additional data provided in the Declaration of Dr. Pietersz under 35 U.S.C. § 1.132 submitted with the last response.

Applicants again traverse the Examiner's rejection on the basis of enablement. The following discussion, associated attachments, and new Declaration of Dr. Pietersz under 35 U.S.C. § 1.132 were not earlier presented because in the prior Office Action mailed on October 23, 2002, the Examiner did not specifically raise the issue of enablement with regard to whether mannose receptor bearing cells were in the composition. In the October 23 Office Action, the Examiner contended that the specification does not enable immunoregulatory compositions comprising any antigen other than MUC1 nor any carbohydrate polymer other than oxidized mannose. Therefore, Applicants addressed the rejection with regard to the antigens and carbohydrate polymers. Applicants respectfully request

that the Examiner consider these arguments and new attachments, which are presented to specifically address the Examiner's concerns with reference to the component of mannose receptor bearing cells.

First, contrary to the Examiner's assertion, the fact that other antigens, when conjugated to mannan, induce an *in vivo* cellular immune response as shown in the previously filed Declaration by Dr Pietersz that was filed with the Amendment and Response dated March 25, 2002), and the two papers by Stambas *et al.*, indicate that mannose receptor bearing cells are already necessarily and inherently involved in this response.

This is because an *in vivo* cellular immune response, such as a T-cell response, begins with antigen processing and presentation by dendritic cells or macrophages to T-lymphocytes for generating a T cell immune response. Dendritic cells and macrophages are antigen presenting cells (APCs) and have mannose receptors on the cell surface. A T-cell response *follows* or results from exposure of dendritic cells or macrophages to the antigen. The Examiner is respectfully referred to the attached copies of relevant pages from the "Handbook of Human Immunology", and particularly to the underlined text.

Accordingly, the *in vivo* T-cell response to administration of non-MUC 1 antigens conjugated to mannan, as shown in the Pietersz Declaration and Stambas *et al* articles, is a true reflection of how the same antigen conjugates would behave after treatment with mannose receptor cells *ex vivo*, followed by administration of the cells to a patient. In other words, with regard to the Examiner's issue pertaining to the antigen, the demonstration that the conjugate works *in vivo* is sufficient to address the expectation of how conjugates comprising non-MUC1 antigens will behave as an *ex vivo* composition that includes the cells. Therefore, the prior evidence is sufficient to enable the invention for the use of antigens other than MUC1 in the claimed composition (which includes the mannose receptor bearing cells).

Second, as already submitted in a prior declaration dated May 11, 2001 by inventor Dr Geoff Pietersz in response to the Office Action mailed February 13, 2001 (Paper No. 15), the presence of at least one mannose unit in the antigen-carbohydrate polymer conjugate is sufficient to provide immunogenicity. See paragraph 5 in the declaration, and particularly the reference, Apostolopoulos et al., *Eur. J. Immunol*, 30: 1714 (2000), which is referred to therein. A further copy of that reference is enclosed for the Examiner's convenience in this discussion. The Examiner's attention

is particularly directed to page 1716, section 2.2.3 entitled "Other receptors", where it is shown that only the mannose receptors on APCs play an important role. Accordingly, the presence of a mannose unit in the carbohydrate polymer, with which an antigen forms a conjugate, will enable that particular conjugate to bind to APCs, and result in presentation of the antigen by APCs *in vivo*, thus stimulating an immunogenic response to the antigen in the way described above and in the subsequent literature.

Thus, Applicants submit that the demonstration of operability of a conjugate comprising an antigen and an oxidised carbohydrate polymer comprising mannose enables the invention claimed, since all the "ingredients" for APC priming are present in the claimed conjugate. The subsequent chain of biological events leading to an immune response such as a T cell response follows from the APC priming as shown in the *in vivo* experiments.

Third, as the Examiner will appreciate, the aim of the present invention is to efficiently induce, or boost a cellular response to antigens so that there is effective vaccination. The Examiner's attention is directed to page 62 lines 1-11 of the present specification, where the effectiveness of the invention is disclosed - the results of Example 1 in the present application show that the *ex vivo* priming of mannose-receptor bearing cells (with antigen-mannan conjugates) induces a CTL (cytotoxic T lymphocyte) response. Further, the response is induced in an efficient manner by requiring only one immunization to increase CTL precursors to a level normally obtained by three immunizations.

Thus, the fact that an *in vivo* T cell response is seen with administration of a non-MUC1 antigen-conjugate would indicate that if the conjugate were treated in accordance with the invention, it would also result in a desired and rapid cellular immune response to the antigen. Consequently, the claims in the present application are fully enabled, particularly in view of the additional data given in the Pietersz Declaration and the Stambas *et al* articles and the reasons above.

Finally, Applicants submit herewith a new Declaration of Dr. Pietersz under 37 CFR 1.132 which contains additional data that show *in vitro* or *ex vivo* pulsing of dendritic cells with mannan-antigen conjugates (where the antigens are not Muc1), and the ability of the pulsed APCs to induce cellular responses in animals. The executed copy of the Declaration will be sent under separate

cover shortly, as Applicant's agent was not able to obtain the copy from the inventor in Australia in time to file this response.

In summary, the evidence already of record clearly demonstrates that the claimed composition is fully enabled, and the additional evidence provided herein further confirms the same. In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 3-17, 19-21, 24-26, 38 and 70 under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 1, 3-17, 19-21, 24-26, 38 and 70 Under 35 U.S.C. § 103:

The Examiner has maintained the rejection of Claims 1, 3-17, 19-21, 24-26, 38 and 70 under 35 U.S.C. § 103, contending that these claims are unpatentable over the combination of Apostolopoulos et al. in view of Koning et al., for the reasons of record. In response to Applicant's argument against the rejection in the last response, the Examiner contends that Applicants' priority document (U.S. Serial No. 08/340,711) did not disclose compositions which comprise the mannose receptor bearing cells along with the conjugate of antigen and carbohydrate polymer. Therefore, the Examiner denies the benefit of priority to the application and has maintained the rejection.

Applicants traverse the Examiner's rejection of Claims 1, 3-17, 19-21, 24-26, 38 and 70 under 35 U.S.C. § 103. The following arguments were not previously submitted because in the October 23 Office Action, the Examiner stated that the rejection was made because the limitation of an "immunoregulatory" composition was allegedly not disclosed or enabled in the parent application, which led Applicants to present the arguments as set forth in the last response. Upon clarification that the Examiner objects to an alleged lack of disclosure with regard to the mannose receptor bearing cells, Applicants again traverse the rejection as follows.

First, the priority claim for this application is discussed. The present application is a continuation-in-part of U.S. Application Serial No. 08/833,807, filed April 9, 1997, which is a continuation of U.S. Application Serial No. 08/340,711, filed November 16, 1994. The '807 and the '711 specifications are identical. As previously discussed, the '711 application (and thus the '807 application) discloses an immunoconjugate which is an oxidized carbohydrate polymer comprising mannose and aldehydes conjugated to an antigen, and which is capable of provoking a cellular immune response. The present application also claims the benefit of priority under 35 U.S.C. §

119(e) from U.S. Provisional Application Serial No. 60/060,594, filed September 29, 1997. The full scope of the claimed invention, including the composition of mannose receptor bearing cells and the recited immunoconjugate are disclosed and enabled by the provisional application.

The Examiner is citing the combination of Apostolopoulos (effective October 1995) and Koning (effective April 1998) against the claims. First, although the parent priority document ('711 application, filed November 1994) does not explicitly disclose mannose receptor bearing cells and accordingly their combination with the conjugate, neither does the cited Apostolopoulos reference, by the Examiner's own admission. As such, the '711 parent application is sufficient to predate the Apostolopoulos reference for the teaching that the cited reference contributes to the combination of cited references.

Second, the Koning reference (published 1998) is being cited for the teaching of using mannosylated antigens to enhance uptake of antigens by mannose receptor bearing cells. However, the present application clearly predates this reference for that teaching (the use of mannose receptor bearing cells) and indeed for the entire claimed invention, via the priority provisional application (filed September 1997).

Therefore, for each teaching in the combination that is used to make the obviousness rejection, the present application predates that teaching through one or more of the application priority documents. Accordingly, neither reference is effective prior art for the teaching alleged by the Examiner. Moreover, given that Koning is not an effective reference at all due to its publication subsequent to the provisional application priority date, regardless of whether or not Apostolopoulos is effective, the combination of references can not be properly cited under 35 U.S.C. § 103.

Further, Applicants note that the Koning reference in no way teaches the conjugation of antigens with carbohydrate polymers comprising mannose units. Koning only teaches direct mannosylation of peptide antigens by chemically introducing a mannose to, e.g., the N-terminal of a peptide. See for example page 4 line 5 and line 34 and in particular, page 11 at "Attachment of the carbohydrate moieties to the peptides." Accordingly, there is no motivation to combine Koning with the Apostolopoulos reference in any event.

In view of the foregoing discussion, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 3-17, 19-21, 24-26, 38 and 70 under 35 U.S.C. § 103.

Rejection of Claim 9 Under 35 U.S.C. § 112, Second Paragraph:

The Examiner has rejected Claim 9 under 35 U.S.C. § 112, second paragraph, contending that this claim is indefinite for reciting "induce mannose receptors". The Examiner questions what is meant by the phrase.

To expedite prosecution, Claim 9 has been amended to recite "induce expression of mannose receptors". Support for this amendment is found in the specification on page 18, lines 4-7.

In view of the foregoing amendment, Claim 9 is believed to be definite and the Examiner is respectfully requested to withdraw the rejection under 35 U.S.C. § 112, second paragraph.

Applicants have attempted to address all of the Examiner's concerns as set forth in the July 29 Office Action, and it is submitted that the claims are in a condition for allowance. In the event that the Examiner has any questions regarding Applicants' position, please consider this to be a provisional request for a telephone interview with the below-named agent.

Respectfully submitted,

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Date: November 27, 2002

In the Claims:

Claim 9 has been amended as shown below.

9. (Twice Amended) The composition of Claim 8, wherein said biological response modifiers induce expression of mannose receptors on a cell capable of expressing said mannose receptors.